

## Asymmetric Organocatalysis

Asymmetric organocatalysis, in which a chiral organic molecule catalyzes an enantioselective transformation, is a rapidly growing field<sup>1,2</sup>. Organocatalysts are widely employed in phase transfer catalysis, kinetic resolutions as well as a variety of asymmetric syntheses. Although many of these reactions have complementary approaches in the well-studied fields of organometallic catalysis and bioorganic catalysis<sup>3</sup>, asymmetric organocatalysis offers several attractive features.

Unlike metal-ligand complexes, organocatalysts generally tolerate aerobic conditions and do not require rigorous exclusion of water. They possess a wider substrate scope than enzymes and can be used in a variety of organic solvents. Organocatalysts can be synthesized or accessed from naturally chiral molecules, and are also amenable to solid phase synthesis and high throughput screening techniques.

Several popular organocatalysts are actually well-known as ligands in organometallic chemistry and can function as asymmetric catalysts themselves. Other types of organocatalysts display characteristics and mechanistic similarities to known bioorganic catalysts and are often referred to as enzyme mimics. A variety of organic molecules have been employed as asymmetric catalysts, particularly the cinchona alkaloids, amino acids and derivatives, small peptide-based molecules as well as heterazolium catalysts.

### Cinchona Alkaloids

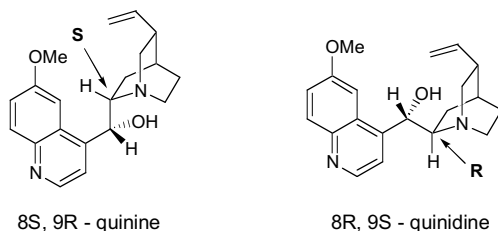


Figure 1. Structures of quinine and quinidine

The cinchona alkaloids represent a class of natural products that possess several important features rendering them useful as asymmetric organocatalysts<sup>4</sup>. They are readily available, inexpensive, and as in the case of diastereomeric pairs such as quinine and quinidine (Figure 1), allow access to either enantiomeric product. Steric constraints imposed by the bulky quinoline and quinuclidine ring systems as well as the presence of

both Lewis acidic and Lewis basic sites have rendered the cinchona alkaloids useful asymmetric catalysts for a variety of transformations.

Their use as nucleophilic catalysts was first described over twenty years ago in an elegant synthesis of  $\beta$ -lactones by Wynberg and Staring<sup>5,6</sup>. This process utilized the nucleophilic nitrogen in the quinuclidine ring to promote a net [2 + 2] cycloaddition between activated aldehydes and ketenes. The reaction between chloral and ketene catalyzed by *O*-acetyl quinidine formed the corresponding  $\beta$ -lactone with *S*-configuration in 89% yield and 98% ee. The reaction is presumed to proceed through a tandem aldol-lactonization process.

Due to the high levels of stereoselectivity achieved, several elaborations on this methodology have been reported. The asymmetric synthesis of bicyclic lactones<sup>7</sup> via an intramolecular aldol-lactonization process catalyzed by *O*-acetyl quinidine as well as the dimerization of methyl

ketene to form optically active polypropionate synthons are two examples<sup>8,9</sup>. Notably, Leckta utilized benzoyl quinine as catalyst for the highly enantioselective preparation of asymmetric  $\beta$ -lactams via an imine-lactamization process. Modest yields (45 – 65%), albeit strong diastereoselectivity (99:1) and excellent enantioselectivity (96 – 99%), resulted for a variety of aryl, alkyl and alkoxy-substituted  $\beta$ -lactams<sup>10</sup>. A particularly interesting example of cinchona alkaloid catalysis has been employed in the first catalytic, highly enantioselective Baylis-Hillman reaction (Figure 2)<sup>11</sup>. Although Baylis-Hillman reactions can be notoriously slow<sup>12,13</sup>, the use of two important reagents, 1,1,1,3,3,3-

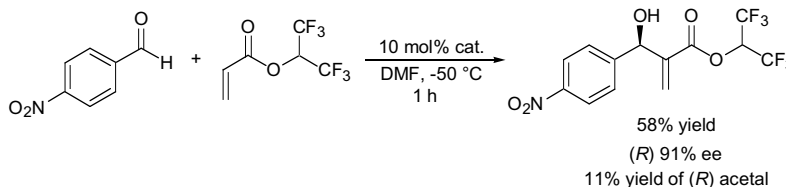


Figure 2. Asymmetric Baylis-Hillman Reaction

hexafluoroisopropylacrylate as an activated alkene and a quinidine-derived catalyst, were found to react with *p*-nitrobenzaldehyde to yield the corresponding (*R*)- $\alpha$ -methylene- $\beta$ -hydroxyester in 58% yield and 91% ee in only one hour.

## Proline

In the early 1970s, two groups, Hajos and Parrish<sup>14</sup> as well as Eder, Sauer and Weichert<sup>15</sup>, independently discovered the asymmetric Robinson annulation of achiral triketones (Figure 3). A small amount of L-proline was found to efficiently catalyze an intramolecular aldol reaction with high yields and excellent

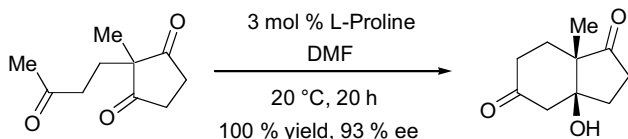


Figure 3. Asymmetric Robinson Annulation catalyzed by L-proline

enantioselectivity. Subsequent investigation led to the proposed mechanism in which an intermediate enamine effectively discriminates between two enantiotopic carbonyl groups<sup>16</sup>. The enamine intermediate implicated in the asymmetric Robinson annulation is reminiscent of the Type 1 aldolases which also mediate aldol reactions via an enamine intermediate<sup>17</sup>. This elegant asymmetric synthesis has proven useful in the synthesis of a variety of steroids and terpenes<sup>18,19</sup>.

List, Lerner and Barbas have reported a direct intermolecular aldol reaction between unmodified acetone and a variety of aldehydes<sup>20,21</sup>. Structure-based catalyst screenings identified L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) as suitable catalysts. The L-proline-catalyzed reaction between isobutyraldehyde and acetone (20 vol%) yielded the  $\beta$ -hydroxy ketone in 97% yield and 96% ee. When hydroxyacetone was employed as an aldol donor, 1,2-*anti* diols were prepared with high levels of enantioselectivity up to 99%<sup>22</sup>. Unbranched aldehydes underwent self-aldolization and yielded lesser amounts of the aldol products<sup>23</sup>.

In these transformation, L-proline functions as a “microaldolase” similar to Type 1 aldolases, and the reaction is presumed to proceed via an enamine intermediate in a well-defined, metal-free Zimmerman-Traxler-type transition state (Figure 4). Unlike most catalytic asymmetric aldol reactions, this variant does not require a preformed enolate. Although 20-30 mol% of L-proline is required, it can be recovered by simple filtration.

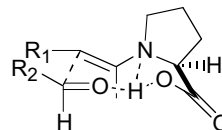


Figure 4. L-proline-catalyzed aldol transition state

L-Proline has also been shown to be an effective catalyst for the direct Mannich reaction between acetone, *p*-anisidine, and a variety of aldehydes<sup>24,25</sup>. The *p*-methoxyphenyl (PMP)-protected amines are isolated in moderate to high yields (35-90%) with good to excellent enantioselectivity (70-96%) from both  $\alpha$ -substituted and  $\alpha$ -unsubstituted aldehydes. The use of hydroxyacetone yields *syn*-1,2-amino alcohols with high levels of enantioselectivity (61-99%). Compared to the direct aldol reaction which yielded *anti*-diastereomers, *syn*-diastereomers arise in the Mannich reaction due to the greater steric interactions between the aryl amine and the pyrrolidine ring of the catalyst. In addition, modest levels of enantioinduction have been achieved when L-proline has been employed as a catalyst in asymmetric Michael additions<sup>26,27,28</sup>.

### Amino Acid Derivatives

The first example of an asymmetric base-catalyzed Diels-Alder reaction was published by Riant and Kagan in which a variety of chiral  $\beta$ -amino alcohols, including those derived from L-proline, were used as catalysts<sup>29,30</sup>. Excellent yields ranging from 85 – 95% were obtained, although with moderate levels of enantioselectivity. Recently, MacMillan and co-workers have employed an organocatalyst derived from phenylalanine in Diels-Alder reactions. The formation of an iminium ion is postulated to lower the lowest-unoccupied molecular orbital (LUMO) of the dienophile.

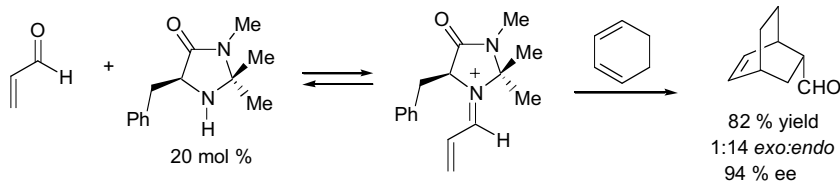


Figure 5. Diels-Alder reaction catalyzed by the formation of a chiral iminium ion

After cycloaddition, hydrolysis of the iminium ion provides the basis for catalytic turnover. Diels-Alder adducts have been obtained in high yields and excellent enantioselectivities for both  $\alpha,\beta$ -unsaturated aldehydes (Figure 5)<sup>31</sup> and ketones<sup>32</sup>. In addition, catalysis via the formation of a reversible iminium ion has proven a general strategy for asymmetric 1,3-dipolar cycloadditions between  $\alpha,\beta$ -unsaturated aldehydes and nitrones<sup>33</sup>, Friedel-Crafts alkylation<sup>34</sup>, indole alkylation<sup>35</sup> as well as the conjugate addition of electron-rich benzenes to  $\alpha,\beta$ -unsaturated aldehydes<sup>36</sup>.

Recently, Corey reported the use of a C-2 symmetric guanidine catalyst derived from phenylglycine to promote the enantioselective addition of hydrogen cyanide to N-benzhydryl imines<sup>37</sup>. The resulting  $\alpha$ -amino nitriles were formed in excellent yields (80 – 99%) and high ee's (50–88%) for aromatic imines. Hydrogen bonding and van der Waals forces between the catalysts and the imine are suggested to explain the high levels of stereoinduction as well as the reversal of configuration when alkyl imines are employed.

### Peptide-based catalysts

Inoue reported the enantioselective addition of hydrogen cyanide to aldehydes catalyzed by a rigid cyclic dipeptide composed of L-phenylalanine and L-histidine<sup>38</sup>. Designed to be a small molecule enzyme mimic of oxynitrilase, the dipeptide catalyzed the formation of the (*R*) cyanohydrin from benzaldehyde in 97% conversion and 97% ee. In contrast to the structural simplicity of the molecule, this reaction displays complex behavior including enantioselective autoinduction and the indication of a non-monomeric catalyst species<sup>39</sup>. Surprisingly, this dipeptide did not catalyze the enantioselective addition of cyanide to aldimines; however, a slight modification of the side chain imidazole to a more basic guanidine yielded a successful catalyst<sup>40</sup>. The role of guanidine likely ensures a tight ion pair between cyanide and the protonated catalyst

prior to nucleophilic addition to the imine. Interestingly, this slight modification from Inoue's original catalyst resulted in opposite facial selectivity for cyanide addition.

Although linear peptides were once considered unsuitable for catalysis due to their flexible nature

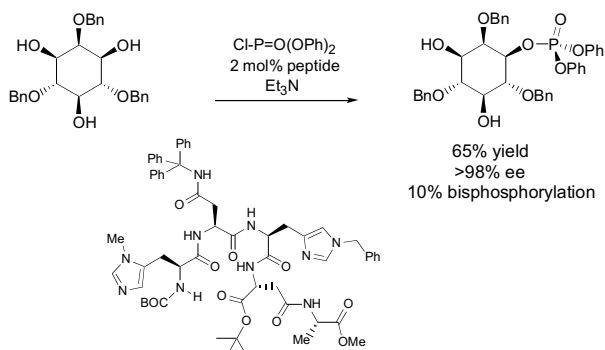


Figure 6. Enantioselective phosphorylation of *meso*-triol

and variable conformation, several recent examples of peptide and peptide-based catalysts for a variety of reactions have been reported. Jacobsen developed a peptide-like catalyst for the asymmetric Strecker reaction which displays high enantioselectivity and broad substrate scope for both aromatic and aliphatic imines<sup>41,42</sup>. NMR studies and molecular modeling support the existence of a well-defined secondary structure adopted by the catalyst in solution<sup>43</sup>. Miller demonstrated that simple  $\beta$ -turn peptides armed with a  $\tau$ -

(benzyl)-histidine residue are enantioselective catalysts for the asymmetric addition of azides to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>44</sup>. The  $\beta$ -azidocarbonyls were shown to undergo subsequent inter- and intramolecular 1,3-dipolar cycloaddition without loss of optical activity<sup>45</sup>. Peptide catalysts have also been shown to promote the enantio- and regio-selective mono-phosphorylation of polyols (Figure 6)<sup>46</sup>. In analogy to histidine-dependent kinases, the reaction may include an intermediate phosphoimidazolium ion that interacts with specific substrate sites in a manner controlled by the peptide's conformation.

## Heterazolium Catalysis

Although Breslow elucidated the mechanism of thiazolium catalysis over forty years ago in the context of the benzoin condensation<sup>47,48</sup>, there have been few successful asymmetric developments based on this approach<sup>49,50,51</sup>. Slight improvements in enantioselectivity were made

with thiazolium catalysis<sup>52</sup>. The most notable accomplishment is a thiazolium-catalyzed asymmetric intramolecular version of the Stetter reaction in which yields and enantioselectivities of up of 70% were obtained (Figure 7)<sup>53</sup>.

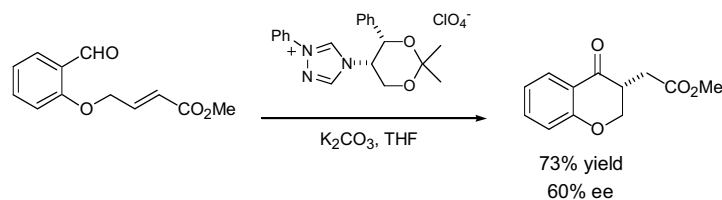


Figure 7. Thiazolium catalysis of the Stetter reaction

## Conclusion

High levels of enantioselectivity have been achieved for a variety of different reactions using simple organic molecules as catalysts. Classic examples include Wynberg's synthesis of  $\beta$ -lactones catalyzed by *O*-acetyl quinidine and the asymmetric Robinson annulation catalyzed by L-proline. Leckta's route to enantioselective  $\beta$ -lactams is especially elegant and could prove useful for the synthesis for a variety of biologically important molecules. Methodology surrounding the development of the direct aldol is exciting; however, the large excess of acetone that is required limits the scope of the reaction. In particular, combinatorial approaches to peptide-based catalysts, such as those developed by Jacobsen and Miller, show scope for future developments. Although organocatalysis does not rival the scope of organometallic catalysis or the selectivity

and efficiency of bioorganic catalysis, it is a growing field that offers an interesting complement to other catalytic approaches.

## References

- 1) Dalako, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. Enantioselective Organocatalysis.
- 2) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. Amino Acids and Peptides as Asymmetric Organocatalysts.
- 3) Groger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529. The Application of L-Proline as an Enzyme Mimic and Further New Asymmetric Syntheses Using Small Organic Molecules as Chiral Catalysts.
- 4) Wynberg, H. *Topics in Stereochem.* **1986**, *16*, 87. Asymmetric Catalysis by Alkaloids.
- 5) Wynberg, H. *J. Am. Chem. Soc.* **1982**, *104*, 166. Asymmetric Synthesis of (*S*)- and (*R*)-Malic Acid from Ketene Chloral.
- 6) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977. Catalytic Asymmetric Synthesis of Chiral 4-Substituted 2-Oxetanes.
- 7) Cortez, G. S.; Tennyson, R. L.; Romo, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 7945. Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions: Catalytic, Asymmetric Synthesis of Bicyclic  $\beta$ -Lactones.
- 8) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006. Catalytic, Asymmetric Dimerization of Methylketene.
- 9) Guo, X. L., W.; Calter, M. A. *Org. Lett.* **2001**, *3*, 1499. One-Pot, Catalytic, Asymmetric Synthesis of Polypropionates.
- 10) Taggi, A. E. H., A. H.; Wack, H.; Young, B.; Drury III, W. J.; Leckta, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. Catalytic, Asymmetric Synthesis of  $\beta$ -Lactams.
- 11) Iwabuchi, Y. N., M; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. Chiral Amine-Catalyzed Asymmetric Baylis-Hillman Reaction: A Reliable Route to Highly Enantiomerically Enriched ( $\alpha$ -Methylene- $\beta$ -Hydroxy)esters.
- 12) Ameer, F.; Drewes, S.; Frees, S.; Kaye, P. T. *Syn. Comm.* **1988**, *18*, 495. Rate Enhancement Effects in the DABCO Catalysed Synthesis of Hydroxyalkenoate Esters.
- 13) Drewes, S. E. R., G. H. P. *Tetrahedron* **1988**, *44*, 4653. Synthetic potential of the tertiary amine-catalyzed reaction of activated vinyl carbanions with aldehydes.
- 14) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry.
- 15) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures.

- 16) Agami, C.; Meynier, G.; Puchot, C. *Tetrahedron* **1984**, *40*, 1031. New Insights into the Mechanism of the Proline-Catalyzed Asymmetric Robinson Cyclization; Structure of Two Intermediates. Asymmetric Dehydration.
- 17) Puchot, c. S., H.; Agami, C. *Tetrahedron Lett.* **1986**, *27*, 1501. Is the Mechanism of the Proline-catalyzed Enantioselective Aldol Reaction Related to a Biochemical Process?
- 18) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Grandi, M. J. D. *J. Am. Chem. Soc.* **1996**, *118*, 28243. Total Synthesis of Baccatin III and Taxol.
- 19) Mickus, D. E. *J. Am. Chem. Soc.* **1992**, *57*, 2732. Synthesis of *ent*-Cholesterol, the Unnatural Enantiomer.
- 20) List, B.; Lerner, R. A.; III, C. F. B. *J. Am. Chem. Soc.* **2000**, *122*, 2395. Proline-Catalyzed Direct Asymmetric Aldol Reactions.
- 21) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. Direct Catalytic Asymmetric Aldol Reaction.
- 22) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. Catalytic Asymmetric Synthesis of *anti*-1,2-Diols.
- 23) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *4*, 573. Proline-Catalyzed Asymmetric Aldol Reactions between Ketones and  $\alpha$ -Unsubstituted Aldehydes.
- 24) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. The Direct Catalytic Asymmetric Three-Components Mannich Reaction.
- 25) Pojarliev, P. B., W. T.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2002**, *124*, 827. The Proline Catalyzed Direct Asymmetric Three-Components Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective Synthesis of 1,2-Amino Alcohols.
- 26) Yamaguchi, M.; Shiraishi, T.; HIRAMA, M. *J. Org. Chem.* **1996**, *61*, 3520. Asymmetric Michael Addition of Malonate Anions to Prochiral Acceptors Catalyzed by L-Proline Rubidium Salt.
- 27) Hanessian, S. *Org. Lett.* **2000**, *2*, 2975. Catalytic Asymmetric Conjugate Addition of Nitroalkanes to Cycloalkenones.
- 28) Betancourt, J. M. S., K.; Rajeswari, T.; Barbas III, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441. Catalytic enantioselective direct Michael additions of ketones to alkylidene malonates.
- 29) Raint, O. K., H. B. *Tetrahedron* **1994**, *50*, 4543. Asymmetric Base-Catalyzed Cycloaddition Between Anthrone and some Dienophiles.
- 30) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403. Asymmetric Diels Alder Reaction Catalyzed by Chiral Bases.

- 31) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction.
- 32) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *124*, 2458. The First General Enantioselective Catalytic Diels-Alder Reaction with Simple  $\alpha,\beta$ -Unsaturated Ketones.
- 33) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition.
- 34) Paras, N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedel-Crafts Alkylation.
- 35) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis.
- 36) Paras, N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. The Enantioselective Organocatalytic 1,4-Addition of Electron-Rich Benzenes to  $\alpha,\beta$ -Unsaturated Aldehydes.
- 37) Corey, E. J. *Org. Lett.* **1999**, *1*, 157. Enantioselective Synthesis of  $\alpha$ -Amino Nitriles from *N*-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst.
- 38) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. The Cyclic Dipeptide *cyclo*[(*S*)-Phenylalanyl-(*S*)-histidyl] as a Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes.
- 39) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740. Enantioselective Autoinduction in the Asymmetric Hydrocyanation of 3-Phenoxy benzaldehyde Catalyzed by *Cyclo*[(*R*)-phenylalanyl-(*R*)-histidyl].
- 40) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. Asymmetric Catalysis of the Strecker Amino Acid Synthesis by a Cyclic Dipeptide.
- 41) Jacobsen, E. N.; Sigman, M. S.; Vachal, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. A General Catalyst for the Asymmetric Strecker Reaction.
- 42) Jacobsen, E. N.; Sigman, M. S. *J. Am. Chem. Soc.* **1998**, *120*, 4901. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries.
- 43) Vachal, P. J., E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction.
- 44) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635. Asymmetric Conjugate Addition of Azide to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds Catalyzed by Simple Peptides.
- 45) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. Asymmetric Azidation-Cycloaddition with Open-Chain Peptide-Based Catalysts. A Sequential Enantioselective Route to Triazoles.

- 46) Sculimbrene, B. M., S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125. Discovery of a Catalytic Asymmetric Phosphorylations through Selection of a Minimal Kinase Mimic: A Concise Total Synthesis of D-*myo*-Inositol-1-Phosphate.
- 47) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. On the Mechanism of Thiamine Action. IV. Evidence from Studies on Model Systems.
- 48) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241. The Mechanism of Thiazolium Catalysis.
- 49) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611. Synthesis of and Asymmetric Induction by Chiral Bicyclic Thiazolium Salts.
- 50) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3615. Synthesis of and Asymmetric Induction by Chiral Polycyclic Thiazolium Salts.
- 51) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925. Catalysis of Benzoin Condensation by Conformationally-Restricted Chiral Bicyclic Thiazolium Salts.
- 52) Breuer, K. E., D. *Helv. Chim. Acta* **1996**, *79*, 1217. A Novel Asymmetric Benzoin Reaction Catalyzed by a Chiral Thiazolium Salt.
- 53) Breuer, K. R., J.; Enders, D. *Helv. Chim. Acta.* **1996**, *79*, 1899. The First Asymmetric Intramolecular Stetter Reaction.